REMARKS

Claims 1-5 and 11-44 are presently pending. Claims 12-41 stand withdrawn from consideration as directed to a non-elected invention. Claims 1-5, 11, 42, 43 and 44 are presently under examination. No claims are amended, added or cancelled herein.

Rejections under 35 U.S.C. § 112, first paragraph

The objection to the specification and corresponding rejection of claims 1-5, 42 and 43 under 35 U.S.C. §112, first paragraph, as containing subject matter not described in the specification so as to enable one skilled in the art to practice the claimed invention is respectfully traversed. Applicants respectfully submit that the specification enables the full scope of claims 1-5, 42 and 43.

The Office Action asserts that, while enabling for compounds in which R^3 is 1-naphtyl, phenylpyrrole, indoloxy and 2-phenyl-5H-thiazole, the specification does not reasonably enable compounds in which R^3 is "any arbitrary derivative" of 1-naphtyl, phenylpyrrole, phenylthiophene, indoloxy or 2-phenyl-5H-thiazole (current Office Action, Paper No. 11, mailed October 3, 2003, section 9 at page 3).

In *Amgen, Inc. v. Hoechst Marion Roussel, Inc*, 232 F.3d 905 (Fed.Cir. 2000), the Federal Circuit clarified the enablement requirement:

> The specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without "undue experimentation."

Id. (citing *Genentech, Inc. v. Novo Nordisk, A/S,* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991))

In *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 47 U.S.P.Q.2d 1705 (Fed. Cir. 1998), the Federal Circuit clearly stated that routine experimentation does not constitute undue experimentation:

> The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Id. (Emphasis added) (citing *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d at 1564, 37 U.S.P.Q.2d at 1623); see also *In re Wands*, 858 F.2d at 736-40, 8 U.S.P.Q.2d at 1403-07.

"[T]he enablement requirement . . . looks to the objective knowledge of one of ordinary skill in the art." *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1050, 34 USPQ2d 1565, 1569 (Fed. Cir. 1995) (citing Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 1532, 3 USPQ2d 1737, 1742 (Fed. Cir. 1987).

Applicants respectfully submit that the specification provides teachings and guidance sufficient to enable the skilled person of ordinary skill to prepare the claimed compound of base claim 1 in which R^3 is a derivative of 1-naphtyl, phenylpyrrole, phenylthiophene, indole or 2-phenyl-5H-thiazole. In particular, the specification teaches features of an R^3 compound by disclosing that the compound R-OH, formed by trypsin cleavage of the compound of formula (I), can be optically distinguished from the compound of formula (I) or reacts with a diazonium salt to form a color in the visible region (specification, page 9, lines 7-10). As further guidance to the skilled person, the specification discloses that representative that R^3 compounds can include a heterocyclic aromatic moiety, where the heterocycle is in a fused ring system and the heteroatom is selected from the group consisting of N and O. Given these teachings, the skilled person would have been able to prepare a compound according to base claim 1 in which R^3 is a derivative of 1-naphtyl, phenylpyrrole, phenylthiophene, indole or 2-phenyl-5H-thiazole and confirm via routine methods, not requiring undue experimentation,

whether the derivative upon trypsin cleavage forms the compound R-OH that either can be optically distinguished from the compound of formula (I) or that reacts with a diazonium salt to form a color in the visible region.

In view of the above, Applicants submit that the specification provides sufficient teachings to enable those in the art to can make and use the invention compositions without "undue experimentation." Accordingly, Applicants respectfully request withdrawal of the objection to the specification and corresponding rejection of claims 1-5, 42 and 43 under 35 U.S.C. §112, first paragraph, as containing subject matter not described in the specification so as to enable one skilled in the art to practice the claimed invention.

Rejections under 35 U.S.C. § 112, second paragraph

The rejection of claims 1-5, 11, 42 and 43 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to point out and distinctly claim the subject matter regarded as the invention. The Office Action asserts that the metes and bounds of the term "derivatives thereof" are unclear. Applicants respectfully disagree and submit that claims 1-5, 11, 42 and 43 are clear and definite to the person of ordinary skill.

Applicants respectfully submit that the U.S. Court of Appeals for the Federal Circuit has indicated in numerous decisions that definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of the prior art, and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. *See, e.g., In re Marosi*, 710 F.2d 799, 218 U.S.P.Q. 289 (Fed. Cir. 1983); *Rosemount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 221 U.S.P.Q. 1 (Fed. Cir. 1984); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983); and *Atmel Corp. v. Information Storage Devices, Inc.*, 198 F.3d 1374, 53 U.S.P.Q.2d 1225 (Fed. Cir. 1999) (district court failed to consider the knowledge of one skilled in the art when interpreting the patent disclosure).

> The primary purpose of the definiteness requirement is to ensure that the claims are written in such a way that they give notice to the public of the extent of the legal protection afforded by the patent, so that interested members of the public, e.g., competitors of the patent owner, can determine whether or not they infringe. That determination requires a construction of the claims according to the familiar canons of claim construction.

All Dental Prodx, LLC v. Advantage Dental Prods., 309 F.3d 774, 779-80, 64 USPQ2d 1945, 1949 (Fed. Cir. 2002) (citations omitted).

The determination of whether a claim is invalid as indefinite "depends on whether those skilled in the art would understand the scope of the claim when the claim is read in light of the specification." *See N. Am. Vaccine, Inc. v. Am. Cyanamid Co.*, 7 F.3d 1571, 1579 (1993) (citation omitted).

With regard to the assertion that the phrase "derivatives thereof" is indefinite, Applicants respectfully submit that this term, viewed by the skilled person in light of the specification and what was known in the art, is sufficiently clear and definite to meet the requirements of paragraph 112.

According to the Federal Circuit, "[M]athematical precision is not required--only a reasonable degree of particularity and definiteness." *Exxon v. US*, 265 F.3d 1371, 1381; 60 U.S.P.Q.2d 1272, 1279 (Fed. Cir. 2001). Applicants submit that clarity regarding the metes and bounds of the claims reciting "derivatives" is provided to the skilled by teaching, for example, at page 9, lines 7-10, that features of an R^3 compound include formation of the compound R^3-OH by trypsin cleavage of the compound of formula (I), such that compound R^3-OH can be optically distinguished from the compound of formula (I) or reacts with a diazonium salt to form a color in the visible region. As further guidance to the skilled person, the specification discloses that representative R^3 compounds can include a heterocyclic aromatic moiety, where the heterocycle is in a fused ring system and the heteroatom is selected from the group consisting of N and O. Given these teachings, the skilled person would have been able to prepare a compound according

to base claim 1 in which R^3 is a derivative of 1-naphtyl, phenylpyrrole, phenylthiophene, indole or 2-phenyl-5H-thiazole and confirm via routine methods, not requiring undue experimentation, whether the derivative upon trypsin cleavage forms the compound R-OH that either can be optically distinguished from the compound of formula (I) or that reacts with a diazonium salt to form a color in the visible region. The skilled person would have understood with clarity that a derivative of 1-naphtyl, phenylpyrrole, phenylthiophene, indole or 2-phenyl-5H-thiazole can be any molecular modification, for example, alteration interatomic distances, provided that the parent aryl retains the stability required to not form the R^3-OH compound absent trypsin cleavage of the compound of formula (I).

Another issue with regard to clarity is the knowledge of one skilled in the art when interpreting the patent disclosure. Notably, the Federal Circuit has overturned cases on the indefiniteness issue where the knowledge of one skilled in the art was not taken into account. *See Atmel Corp. v. Information Storage Devices, Inc.*, 198 F.3d 1374, 53 U.S.P.Q.2d 1225 (Fed. Cir. 1999). Applicants respectfully submit that strategies for the manufacture of derivatives and design of analogs of nonprotein molecules were known to the skilled person at the time of the present invention. As evidence that the design and preparation of derivatives of nonprotein molecules was routine known in the art at the time the above-identified application was filed, Applicants submit as Attachment A to this paper, Cannon, Analog Design, in "Burger's Medicinal Chemistry and Drug Discovery" Vol. 1 (ed. M.E. Wolff; John Wiley & Sons 1995), pages 783-802. Given the knowledge in the art with regard to the molecular modifications used to prepare a derivative or analog design, the skilled person would have understood with clarity the metes and bounds of claims reciting a derivative of 1-naphtyl, phenylpyrrole, phenylthiophene, indole or 2-phenyl-5H-thiazole. Therefore, Applicants submit that, when read in light of the specification, the claims 1-5, 11, 42 and 43, reasonably apprise those skilled in the art of the scope embraced by the presently claimed invention.

Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1-5, 42 and 43 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to point out and distinctly claim the subject matter regarded as the invention.

CONCLUSION

In light of the foregoing Remarks, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to contact the undersigned attorney with any questions related to this application.

Respectfully submitted,

Astrid R. Spain

Date: December 30, 2003

Astrid R. Spain
Registration No. 47,956
Telephone: (858) 535-9001
Facsimile: (858) 535-8949

McDERMOTT, WILL & EMERY
4370 La Jolla Village Drive, Suite 700
San Diego, California 92122

Attachment:
Attachment A - Cannon, "Analog Design," Burger's Medicinal Chemistry and Drug Discovery, (ed. M.E. Wolff; John Wiley & Sons) 1:783-802 (1995).

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hers,

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CHAPTER NINETEEN

Analog Design

JOSEPH G. CANNON

University of Iowa
Iowa City, Iowa, USA

CONTENTS

1 INTRODUCTION

This chapter is limited to nonprotein therapeutic candidates. The rapidly evolving field of peptide analogs and peptidomimetic agents merits and requires separate and extensive consideration. In any strategy aimed at designing new drug molecules or analogs of known biologically active compounds, there are no absolute rules for procedure or guidelines; the knowledge, imagination, and intuition of the medicinal chemist are the most important factors for success. Analog design is as much an art as it is a science. The concept of analog design presupposes that a lead has been obtained, i.e., a chemical compound has been identified that possesses a desirable pharmacological property. The search for and identification of leads is a challenge and is a separate topic. It is sufficient for the present discussion to note that lead compounds are frequently identified as endogenous participants (hormones, neurotransmitters, second messengers, or enzyme cofactors) in the body's biochemistry and physiology, or a lead may result from routine, random biological screening of natural products or of synthetic organic molecules that were

Burger's Medicinal Chemistry and Drug Discovery, Fifth Edition, Volume 1: Principles and Practice, Edited by Manfred E. Wolff.
ISBN 0-471-57556-9

ATTACHMENT A

created for purposes other than for use as drugs.

Analog design is most fruitful in the study of pharmocologically active molecules that are structurally specific: their biological activity depends on the nature and the details of their chemical structure. Hence, seemingly minor modification of the molecule may result in a profound change in pharmacological response (increase, diminish, completely destroy, or alter the nature of the response). In pursuing analog design and synthesis, it must be recognized that the newly created analogs are different chemical entities from the lead compound. It is not possible to retain all and exactly the same solubility and solvent partition characteristics, chemical reactivity and stability, acid or base strength, and/or *in vivo* metabolism properties of the lead compound. Thus, although the new analog may demonstrate pharmacological similarity to the lead compound, it is not likely to be identical to it, nor will its similarities and differences always be predictable.

The goal of analog design is twofold: (*1*) to modify the chemical structure of the lead compound to retain or reinforce the desirable pharmacologic effect while minimizing unwanted pharmacological (e.g., toxicity, side effects, or undesirable metabolism) and physical and chemical properties (e.g., poor solubility and solvent partitioning characteristics or chemical instability), which may result in a superior therapeutic agent; and (*2*) to use target analogs as pharmacological probes (i.e., tools used for the study of fundamental pharmacological and physiological phenomena) to gain greater insight into the pharmacology of the lead molecule and perhaps to reveal new knowledge of basic biology. Studies of analog structure–activity relationships may increase the chemist's ability to predict optimum chemical structural parameters for a given pharmacological effect.

Analog design is greatly facilitated if the chemist can initially define the pharmacophore of the lead compound: that combination of atoms within the molecule that is responsible for eliciting the desired pharmacologic effect. Analog design may be directed toward maintaining this combination of atoms intact in a newly designed molecule or toward a carefully planned, systematic modification of the pharmacophore. If the chemist is uncertain about the composition of the pharmacophoric portion of the molecule, a prime initial goal of analog design should be to define the pharmacophore. The chemist addresses the following questions: What change(s) can be made in the lead molecule that permit(s) retention or reinforcement of the basic pharmacological action? and What change can be made in the molecule that diminishes, destroys, or qualitatively changes the basic pharmacological action? The ideal program of analog design should involve a *single* structural change in the lead molecule with each new compound designed and synthesized. An analog in which multiple changes in the structure of the lead molecule have been made simultaneously may occasionally produce a molecule with highly desirable pharmacologic effects but relatively little useful information will be gained from such a molecule. It cannot be readily determined which change (or which combination of changes) was responsible for the enhancement of the desired pharmacology. On a practical basis, it is frequently chemically impossible to effect only one discrete change in the lead molecule; one simple molecular structural alteration will influence many structural and chemical parameters. Nonetheless, the chemist should be cognizant of the disadvantages inherent in "shotgun" modification of lead molecules.

In analog design, molecular modifications of the lead compound can involve one or more of the following strategies:

1. Bioisosteric replacement.
2. Design of rigid analogs.

3. Homologati ation of cha matic ring p tion of ring
4. Alteration c of geometri
5. Design of f cule that c group (bon
6. Alteration c in the pharr parts of the

None of these ferable to the c attention and c combinations c molecule ma Considering th combinations possible within obvious that can be design pound is larg that might b impossible, e. of existence, o ingly formidab negative facto tion of possib for synthesis; always be con target molecu molecule. Rat concerning w synthesized, a be established reasonable th equal, the ch less challengi truism, the ch or her intuitic and applicatic fication strate structure of t certain extent to be studied.

3. Homologation of alkyl chain(s) or alteration of chain branching, design of aromatic ring position isomers, and alteration of ring size.
4. Alteration of stereochemistry, or design of geometric isomers or stereoisomers.
5. Design of fragments of the lead molecule that contain the pharmacophoric group (bond disconnection).
6. Alteration of interatomic distances within the pharmacophoric group or in other parts of the molecule.

None of these strategies is inherently preferable to the others; all merit the chemist's attention and consideration. Application of combinations of these strategies to the lead molecule may be highly advantageous. Considering the possible permutations and combinations of these changes that are possible within a single lead molecule, it is obvious that the number of analogs that can be designed from a single lead compound is large. Some structural changes that might be proposed are chemically impossible, e.g., the molecule is incapable of existence, or it represents an overwhelmingly formidable synthetic challenge. These negative factors will diminish the population of possible analogs to be considered for synthesis; nevertheless, the chemist will always be confronted with myriad possible target molecules, resulting from a lead molecule. Rational decisions must be made concerning which compounds should be synthesized, and synthetic priorities must be established for target compounds. It is reasonable that, all other factors being equal, the chemist should synthesize the less challenging targets first. Beyond this truism, the chemist's best resources are his or her intuition and imagination. Selection and application of specific molecular modification strategies depends on the chemical structure of the lead compound and, to a certain extent, on the pharmacologic action to be studied.

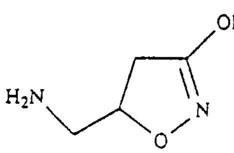
All of the strategies of analog design as well as subsequent decisions concerning target compounds to be synthesized can be facilitated by computer-assisted molecular modeling techniques, which may give the chemist further insights into structural, stereochemical, and electronic implications of the proposed molecular modification.

2 BIOISOSTERIC REPLACEMENT

The concept of bioisosterism derives from the observation that certain physical properties of chemically different substances (e.g., carbon monoxide and nitrogen and ketene and diazomethane) are strikingly similar (1). These similarities were rationalized on the basis that carbon monoxide and elemental nitrogen each have 14 orbital electrons, and similarly, diazomethane and ketene each have 22 orbital electrons. Medicinal chemists have expanded and adapted the original concept to the analysis of biological activity. The following definition has been provided: "Bioisosteres are groups or molecules which have chemical and physical properties producing broadly similar biological properties" (2). This definition might be expanded to include the concept that bioisosteres may produce opposite biological effects, and these effects are frequently a reflection of some action on the same physiological process or at the same receptor site. Bioisosteric similarity of molecules is commonly assigned on the basis of the number of valence electrons of an atom or a group of atoms rather than on the number of total orbital electrons, as was originally specified by Langmuir. In a remarkable number of instances, compounds result that have similar (or even diametrically opposite) pharmacologic effects to the parent compound. The significant concept is that the bioisosteres are affecting, in some fashion, the same receptor site or pharmacological mechanism.

Categories of classic isosteres have been illustrated (2) (Table 19.1).

Dihydromuscimol 1 and thiomuscimol 2 are cyclic analogs of γ-aminobutyric acid (GABA) in which the C=N moiety of the heterocyclic ring is bioisosteric with the C=O of GABA. In addition, the -S- moiety of thiomuscimol is bioisosteric with the ring -O- of dihydromuscimol. Both structures (1) and (2) are highly potent agonists at GABA-A receptors (3). A classic bioisosteric replacement study was reported for a methoxytetrahydropyran-derived inhibitor (4) of 5-lipoxygenase (4) (Table 19.2). None of the isosteric replacements was as potent as the lead compound (4). However, the thio isostere (5) approaches the oxygen compound (4) in potency, and



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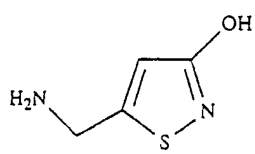
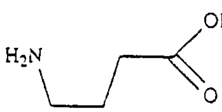
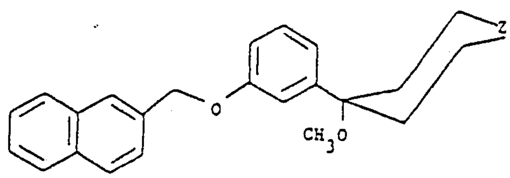


(2)



(3)

Table 19.2 Inhibition of 5-Lipoxygenase



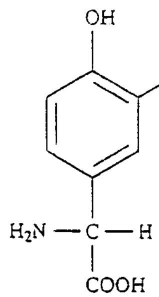
Structure	Z	IC_{50} (μM)
(4)	O	0.07
(5)	S	0.4
(6)	CH_2	2.6
(7)	C=O	3.4
(8)	SO	4.2
(9)	SO_2	10.6
(10)	NCH_3	>40

Table 19.1 Bioisosteric Atoms and Groups

1. *Univalent*	–F	—OH	$-NH_2$	$-CH_3$	–Cl
			–SH	PH_2	
			–I	t-C_4H_9	
			–Br	$-i-C_3H_7$	
2. *Bivalent*	–O–	–S–	–Se–	$-CH_2-$	–NH–
	COOR	COSR	$COCH_2R$	CONHR	
3. *Tervalent*			–N=	–CH=	
			–P=	–As=	
4. *Quadrivalent*			–C– (tetravalent)	–Si– (tetravalent)	
5. *Ring equivalents*	–CH=CH–		–S– (e.g., benzene-thiophene)		
	=CH–		=N– (e.g., benzene-pyridine)		
		–O–	–S–	$-CH_2-$	–NH–

subsequent studies may reveal other advantages of the sulfur compound as a theraputic agent candidate.

Because of its bioisosteric similarity to the normal substrate L-dopa (11), L-mimosine (12) inhibits the enzyme tyrosinase (5). These compounds exemplify a situation in which bioisosteres display *opposite* pharmacological effects at the same receptor.



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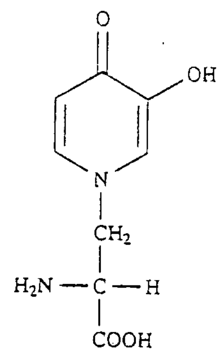
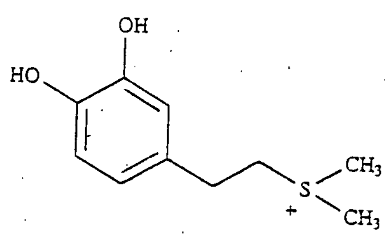


(12)

The sulfonium isostere (13) of *N*,*N*-dimethyldopamine (14) retains the dopaminergic agonist effect displayed by structure (14) (6).

The fact that structure (13) bears a permanent unit positive charge was invoked in support of the hypothesis that β-phenethylamines such as structure (14) interact with the dopamine receptor(s) in their protonated (cationic) form.

Bioisosteric replacement strategy has



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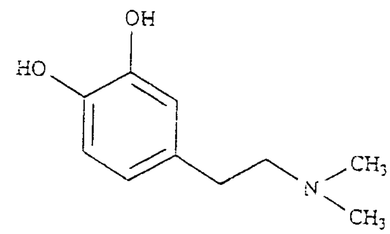
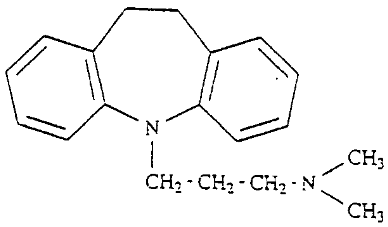


(14)

been fruitful in design of tricyclic antidepressants, using the dibenzazepine derivative imipramine (15) as the lead.

The structural similarity between imipramine (15) and the phenothiazine antipsychotics [typified by chlorpromazine (16)] is apparent. Although these two bioisosteric molecules have different pharmacological uses and likely have different mechanism and sites of action in the central nervous system (7), they share the property of being psychotropic agents. In the antidepressant dibenzocycloheptene derivative amitriptyline (17), the ring nitrogen of imipramine is replaced by an exocyclic olefinic moiety. Demexiptiline (18), doxepin (19), and dothiepin (20) represent other bioisosteric modifications of imipramine that possess antidepressant activity (8).

While the strategy of bioisosteric replacement may be a powerful and highly productive tool in analog design, Thornber (2) has emphasized that fundamental chemical and physical chemical changes will result from this molecular modification, which may in themselves profoundly affect the pharmacological action of the resulting molecules. Possible modifications include change in size of the atom involved in the bioisosteric replacement, change in the shape of the substituted group and possible resulting change in the shape of the entire molecule, differences in bond angles, change in partition coefficient, change in pK_a of the molecule; alteration of chemical reactivity and chemical stability of the



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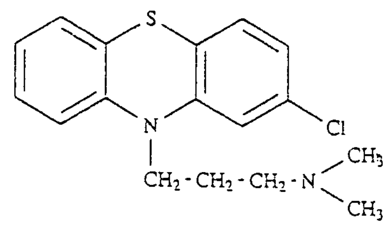

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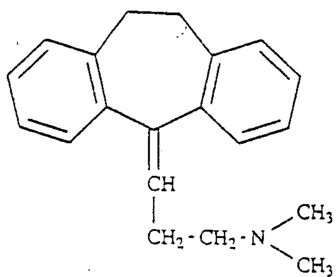

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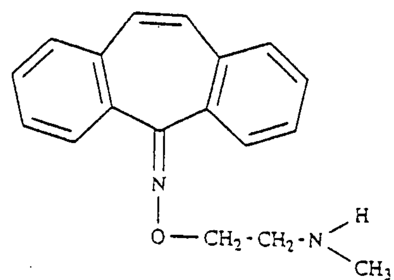

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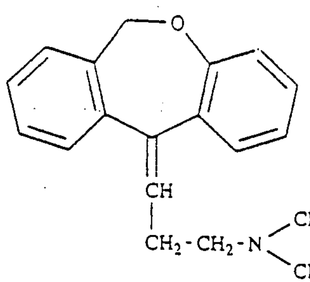

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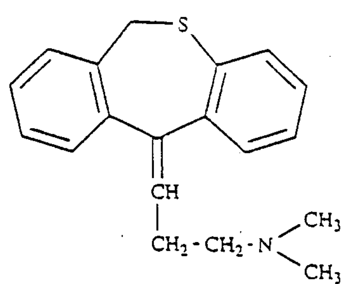


(20)

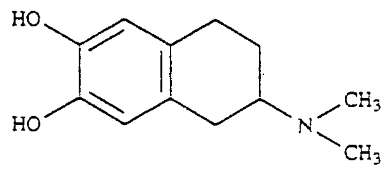
molecule with accompanying alteration of the nature of *in vivo* metabolism of the molecule, and change in hydrogen bonding capacity. The effect and pharmacological significance of many of these parameters are unpredictable and must be determined experimentally.

3 RIGID ANALOGS

Imposition of some degree of molecular rigidity into a flexible organic molecule (by incorporation of elements of the flexible molecule into a rigid ring system or by introduction of a carbon–carbon double or triple bond) may result in potent, biologically active agents that show a higher degree of specificity of pharmacological effect. There are two possible advantages to this technique (9): the three-dimensional geometry of the pharmacophore can be determined and the key functional groups are held in one position, or in the case of a semirigid structure, these groups are constrained to a limited range of steric dispositions and interatomic distances. By the rigid analog strategy, it is possible to approximate "frozen" specific conformations of a flexible lead molecule, which may

provide enhanced pharmacological effect and may assist in defining and understanding structure–activity parameters. Computer-based molecular modeling has been shown to be a useful tool in designing rigid analogs.

The semirigid tetralin congeners (21, 22) of *N*,*N*-dimethyldopamine (14) represent different rotameric conformations of the aromatic ring of dopamine as the aromatic ring relates to the ethylamine side chain when the ring and the side chain are coplanar. Structural constraints of the tetralin ring system impose this restricted geometry on the dopamine moiety. Compounds (21) and (22) display different spectra of effects at different subpopulations of dopamine receptors (10) which likely reflect different conformations assumed by the flexible dopamine molecule at its various *in vivo* sites of action.



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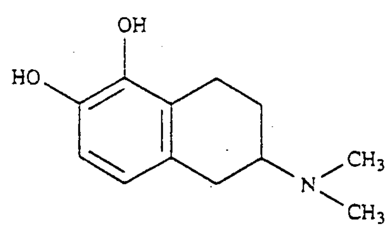
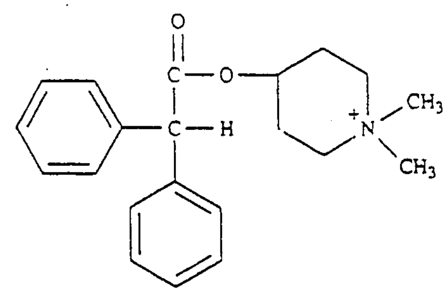


(22)

Restriction of conformational freedom of the acyl moiety in 4-DAMP (23) (an antimuscarinic compound displaying higher affinity at ileal M_3 acetylcholine receptors than at atrial M_2-receptors) was imposed by the structure of the spiro-compound (24) (11).



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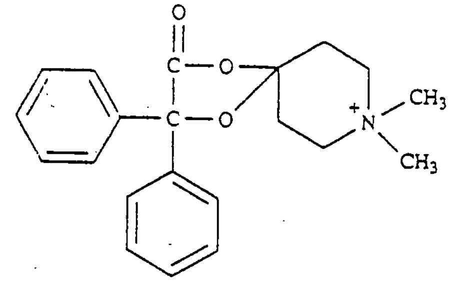
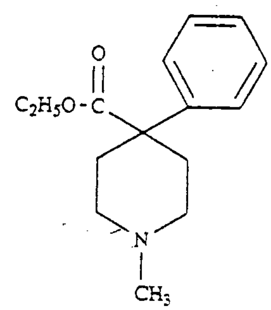


(24)

Spiro-DAMP (24) was slightly more potent at M_2 muscarinic receptors than at M_3 receptors. It was proposed that the geometry of the spiro-molecule might reflect the receptor-bound conformation of 4-DAMP (23); this conformation differs from that observed in the crystal structure of 4-DAMP.

Imposition of rigidity into the piperidine ring of meperidine (25) by introduction of a methylene group between carbons 3 and 6 resulted in the epimers (26) and (27), frozen conformations of meperidine (12).



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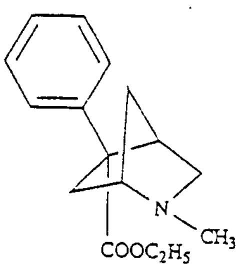

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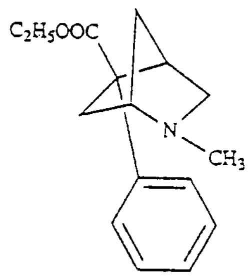
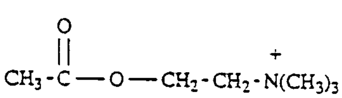


(27)

Isomer (27) was six times as potent as isomer (26), and it was twice as potent as meperidine itself.

Incorporation of the choline portion of the neurotransmitter acetylcholine (28) into a cyclopropane ring system resulted in cis- and trans-1,2-disubstituted molecules (29), (30) in which the acetylcholine molecule is frozen into folded ("cisoid") and extended ("transoid") conformations.



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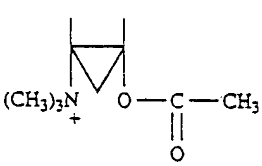

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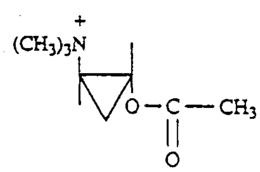

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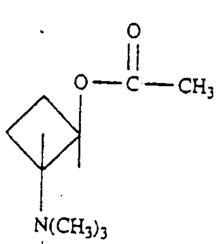
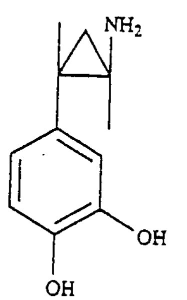


(31)

The (1*S*), (2*S*)-(+)-trans-isomer (30) was somewhat more potent than acetylcholine itself in assays for muscarinic agonism (13) and it was an excellent substrate for acetylcholinesterase. The (±)-cis-isomer (29) was almost inert at muscarinic and nicotinic receptors and was a poor substrate for acetylcholinesterase. These data were taken as evidence that the flexible acetylcholine molecule interacts with muscarinic receptors in an extended geometry of the chain of atoms (14). When this semirigid analog strategy for acetylcholine was applied to a cyclobutane ring system [compound (31)], there was a marked loss of pharmacological effect (15). This result is enigmatic; differences in interatomic distances and bond angles in the pharmacophoric moiety as well as differences in the amount of extraneous molecular bulk seem insufficient to account for the dramatic difference in pharmacological potencies between the three- and the four-membered ring systems.

The cyclopropane ring has been employed to impart a degree of rigidity to the side chain of dopamine [structures (32), (33)] (16).



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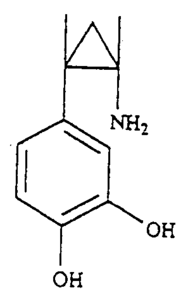

(33)

Neither isomer displayed effects at dopamine receptors, but both were α-adrenoceptor agonists, with the (±)-trans-isomer (32) approximately five times more potent than (±)-cis-isomer (33). It has been suggested (17) that these findings are significant in solving the problem of the

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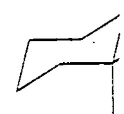

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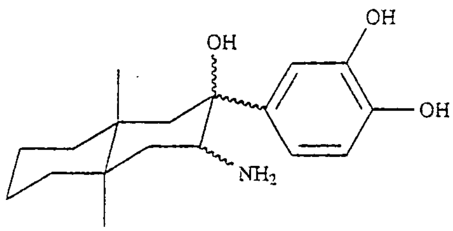
The β-phenylethanolamine moiety was incorporated into the *trans*-decalin ring system (34) and the racemic modifications of all four possible isomers were prepared as significant frozen conformations of the flexible norepinephrine molecule (18). All four compounds displayed approximately equal (extremely low) potency. The achievement of conformational integrity by incorporation of a flexible pharmacophore into a bulky, complex molecule may be at the expense of biological activity.

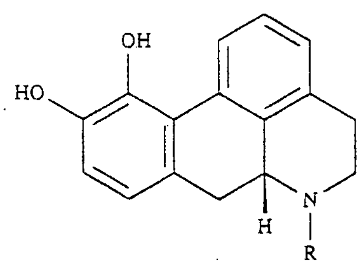


(34)

4 HOMOLOGATION OF ALKYL CHAIN OR ALTERATION OF CHAIN BRANCHING, CHANGES IN RING SIZE, AND RING POSITION ISOMERS

Change in the size or branching of an alkyl chain on a bioactive molecule may have a profound (and sometimes unpredictable) effect on physical and pharmacological properties. An increase in the number of carbons in a chain may significantly increase the lipophilic character of the molecule and change the partition coefficient, which may be reflected in the biology of the compound: alteration of absorption, transport, and excretion properties. Alteration of the size and/or shape of an alkyl substituent can affect the conformational preference of a flexible molecule and may alter the spatial relationships of the components of the pharmacophore, which may be reflected in the ability of the molecule to achieve complimentarity with its receptor or with the catalytic surface of a metabolizing enzyme. The alkyl group itself may represent a binding site with the receptor (via hydrophobic interactions), and alteration of the chain may alter its binding capacity. Conversely, extension of an alkyl chain or branching of it may introduce sufficient extraneous bulk into the molecule to interfere with its optimal interaction with the receptor or with metabolizing enzymes. Position isomers of substituents (even alkyl groups) on aromatic rings may possess different pharmacological properties. In addition to their ability to alter electron distribution in an aromatic ring system, position isomers may differ in their complimentarity to *in vivo* receptors, and a substituent position on a ring may influence the spatial occupancy of the ring system with respect to the remainder of a conformationally variable molecule, What sometimes has been trivialized and denigrated as "methyl group roulette" may indeed be an important parameter in the design of analogs.

Homologation of the *N*-alkyl chain in norapomorphine 35 from methyl (36) to ethyl (37) to *n*-propyl (38) produced increases in emetic action in dogs and in

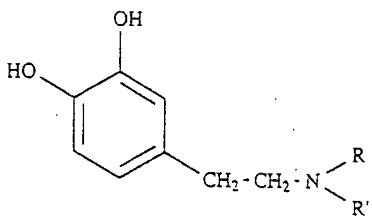


(35) R = H (38) $R = n\text{-}C_3H_7$

(36) $R = CH_3$ (39) $R = n\text{-}C_4H_9$

(37) $R = C_2H_5$

stereotypy responses in rodents (19, 20). The homolog, *n*-butyl (**39**) demonstrated a tremendous loss in potency and activity compared with the lower homologs (20). Studies of *N*,*N*- dialkylated dopamines (**40**)–(**43**) revealed that combinations of alkyl groups may impart a high degree of dopamine agonist effects (21).



(**40**) R = R′ = CH_3

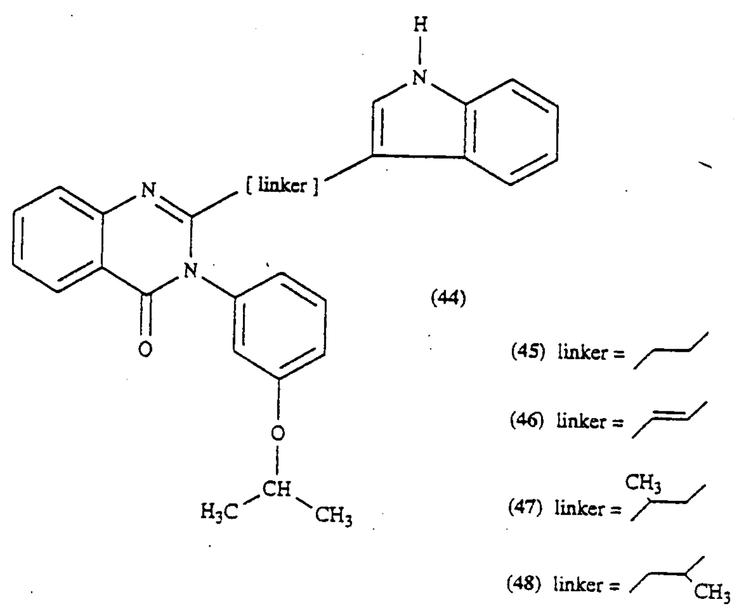
(**41**) R = R′ = n-C_3H_7

(**42**) R = n-C_3H_7; R′ = n-C_4H_9

(**43**) R = R′ = n-C_4H_9

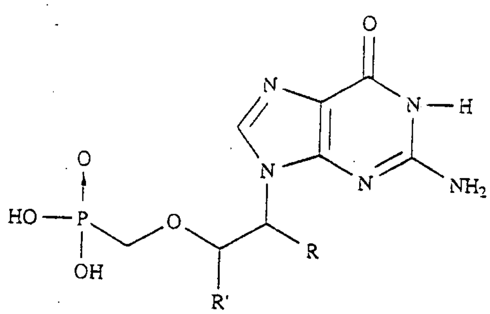
Thus, *N*,*N*-dimethyldopamine (**40**) is extremely potent in certain assays for dopaminergic agonism, and *N*,*N*-di-*n*-propyldopamine (**41**) (22) and *N*-*n*-propyl-*N*-*n*-butyldopamine (**42**) (23) are potent dopaminergic agonists, whereas *N*,*N*-di-*n*-butyldopamine (**43**) is inert (22). It seems likely that the enhanced dopaminergic agonist effects conferred by *N*-ethyl and *n*-propyl groups on aporphine and β-phenethylamine-derived molecules are not related merely to enhanced lipophilic character or to partitioning phenomena, but rather to the likelihood that the 2- and 3-carbon chains have a positive affinity for subsites on certain dopamine receptors. These receptor subsites do not accommodate longer chains (e.g., *n*-butyl).

The alkyl linker between the two heterocyclic ring systems in compound (**44**) was modified in studies of the ability of analogs to bind to the cholecystokinin-B receptor (24). When this linking group was ethylene (**45**), extremely potent receptor binding resulted. Introduction of carbon–carbon unsaturation into the linker (**46**) resulted in a 16-fold decrease in binding ability; this suggests a deleterious effect of conformational restriction and limitation of molecular flexibility on biological activity. Branching of the linker chain with a methyl



group adjacent to the quinazolinone ring (47) produced a 350-fold decrease in binding potency. However, chain branching with a methyl group in the alternate position on the dimethylene chain produced a compound (48) whose potency was of the same order of magnitude as the extremely potent lead compound (45). The exponential difference in receptor binding ability exhibited by the two isomeric-branched chain-linker compound (47) and (48) was ascribed to unfavorable steric interactions between the receptor and the linker methyl group of structure 47 (24). Isomers such as structures (47) and (48) may generate useful computer-generated molecular modeling data with respect to the preferred conformation of the ligand for optimum receptor interaction and the definition of receptor topography.

A study (25) of (phosphonomethoxy) ethylguanidines (49)–(52) as antiviral agents revealed that branching of the ethylene chain by introduction of a methyl at position 1′ (51) diminished antiviral activity 25-fold and diminished toxicity 16-fold compared to the unmethylated system (49).



(49) R = R' = H

(50) R = H ; R' = CH_3

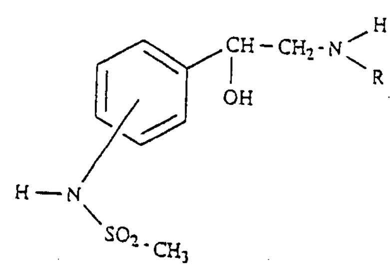
(51) R=CH_3 ; R' = H

(52) R = H ; R' = *gem* - di - CH3

In contrast, (*R*)-(**50**), the 2′-methyl congener, exhibited only a 5-fold decrease in antiviral potency as compared to compound (49), but it also exhibited a 30-fold lessening of toxicity to provide a substantial increase in therapeutic index over compound (49). The 2′, 2′-*gem*-dimethyl congener (52) was somewhat less potent than the (*R*)-2′-monomethyl compound (50) and was markedly more toxic. The (*S*)-2′-methyl analog (50) exhibited a decidedly lower therapeutic ratio than its (*R*)-enantiomer, demonstrating pharmacological difference between stereoisomers.

Closely related to the alteration of chain length and/or branching is alteration of ring size. A methoxytetrahydrofuran derivative (53) (Table 19.3) showed activity as an inhibitor of 5-lipoxygenase (4). The size of the oxygen-containing ring as well as the position of the oxygen member with respect to the methoxy and aryl substituents was varied, as shown in Table 19.3. The (seven-membered) oxepane ring derivative (58) and the (six-membered) tetrahydropyran ring derivative (57) showed enhanced potency over the tetrahydrofuran lead compound (53).

In a series of arylsulfonamidophenethanolamines (59) (26), derivatives bearing the sulfonamido group meta to the ethanolamine side chain displayed properties of a β-adrenoceptor partial agonist, whereas those bearing the sulfonamido group in the para position were β-antagonists (26).



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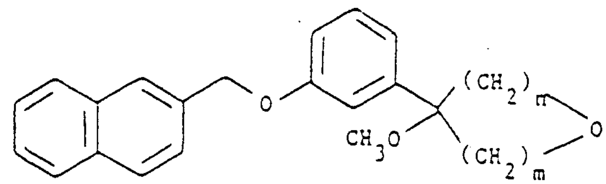
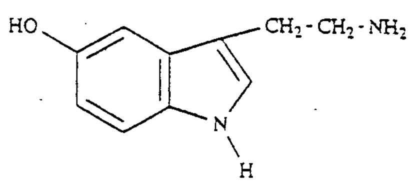
The phenolic group of serotonin (**60**) was incorporated into a pyran ring (**61**) (27), which represents an alkyl substituent at position 4 of the indole ring system.

Table 19.3 Inhibition of Lipoxygenase



Structure	n	m	IC_{50} (μM)
(53)	1	2	0.7
(54)	1	1	2.5
(55)	1	3	1.7
(56)	1	4	2.5
(57)	2	2	0.07
(58)	2	3	0.2



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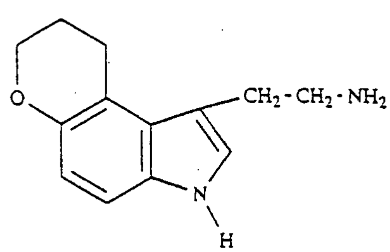

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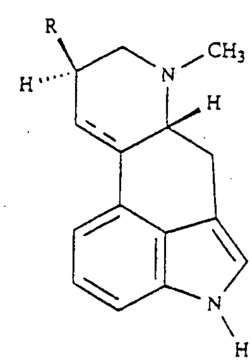

(62)

This analog lost serotonin-like affinity for $5\text{-}HT_1$ receptors, but it is potent and selective for $5\text{-}HT_2$ receptors. The low affinity for $5\text{-}HT_1$ receptors was rationalized, in part, on the basis of steric interference between the dihydropyran ring and the aminoethyl side chain which inhibits the tryptamine system from assuming the folded "ergot alkaloid-like" conformation, as illustrated in structure (**62**), which probably approximates the conformation of serotonin at $5\text{-}HT_1$ receptors.

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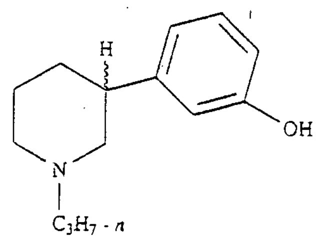
5 ALTERATION OF STEREOCHEMISTRY AND DESIGN OF STEREOISOMERS AND GEOMETRIC ISOMERS

The earlier, almost universally accepted, opinion that, in the case of chiral molecules one enantiomer would be expected to demonstrate pharmacological activity and the other enantiomer should be expected to be pharmacologically inert is not valid. It must be anticipated that all stereoisomers of an organic molecule will exhibit frequently widely different and unpredictable pharmacological effects.

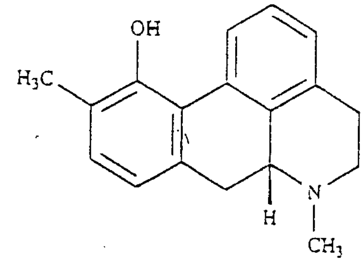
(±) - 3 - (3 - Hydroxyphenyl) - *N* - *n* - propylpiperidine ("3-PPP") (**63**) was described (28) as having highly selective action at dopaminergic autoreceptors.



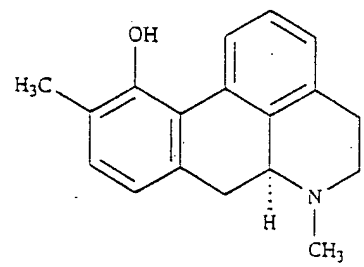
(**63**)

This racemate was resolved (29). At high doses the (*R*)-enantiomer selectively stimulated presynaptic dopaminergic receptor sites, while at lower doses, it selectively stimulated postsynaptic receptor sites. In contrast, the (*S*)-enantiomer stimulated presynaptic dopamine receptors and at the same dose level, it blocked postsynaptic dopamine receptors. Thus this enantiomer exhibits a bifunctional mode of dopaminergic attenuation, that of presynaptic agonism and postsynaptic antagonism. The pharmacological effects of the racemic modification are the sum total of the complex activities of the two enantiomers, and the observed pharmacology of racemic 3-PPP is not an accurate reflection of the pharmacological potential of the individual enantiomers. Pharmacological testing of only a racemic modification is inadequate and may be misleading.

(*R*) - (−) - 11 - Hydroxy - 10 - methylaporphine (**64**) is a highly selective serotonergic 5-HT_{1A} agonist (30).



(**64**)

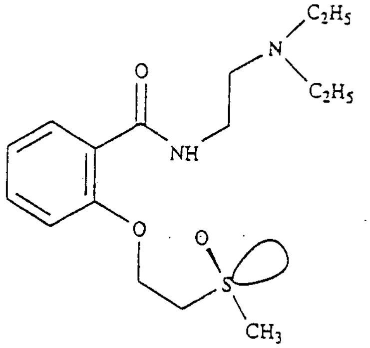


(**65**)

Remarkably, the (*S*)-enantiomer (**65**) is a potent antagonist at this same subpopulation of serotonin receptors (31). The phenomenon of enantiomers which possess opposite effects (agonist–antagonist) at the same receptor, once considered to be extremely rare, has recently been noted more often, probably due to the increasing recognition by chemists and pharmacologists that each member of an enantiomeric pair may possess its own unique and unpredictable pharmacology.

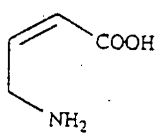
In addition to stereochemistry about a carbon center, other potentially chiral atoms offer possibilities for pharmacological significance. A gastroprokinetic com-

pound (66) with serotonergic activity bears a chiral sulfoxide moiety (32). The enantiomers are equipotent, but the (*S*)-isomer demonstrates a greater intrinsic activity than the (*R*).



(66)

cis- and *trans*-4-Aminocrotonic acids (67), (68) were prepared (33) as congeners of γ-Aminobutyric acid (GABA) (3).



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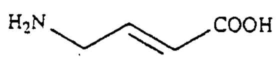

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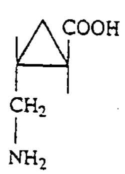

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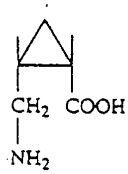
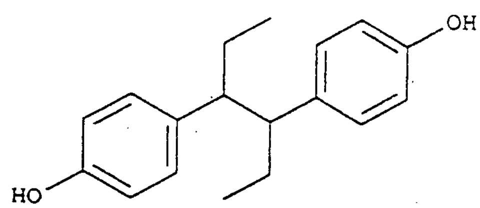


(70)

The folded *cis*-isomer (67) was inert in assays for GABA agonism, whereas the extended *trans*-isomer (68) was active. These data demonstrate biological differences of geometric isomers, which in turn involve yet another structural parameter: imposition of a degree of structural rigidity upon the molecule. A parallel strategy to the *cis*/*trans* GABA congeners (67) and (68) addressed *cis*- and *trans*-1,2-disubstituted cyclopropane derivatives (69) and (70) whose relative effects at GABA receptors paralleled those of the olefinic derivatives (34).

Hexestrol (71), the saturated congener of diethylstilbestrol (72), is the *meso*-form of the molecule. It has the greatest estrogenic potency of the three possible stereoisomers (35). In diethylstilbestrol (72), the E-isomer (trans), has 10 times the estrogenic potency of the Z-isomer (cis); this effect has been rationalized because the E-geometric isomer is an open chain analog of the natural estrogen estradiol (73) (36). In dienestrol (74), the geometric isomerism possible with olefinic moieties has been invoked to achieve a similar kind of open chain analogy to the steroid ring system as in diethylstilbestrol, and a high level of estrogenic activity results.



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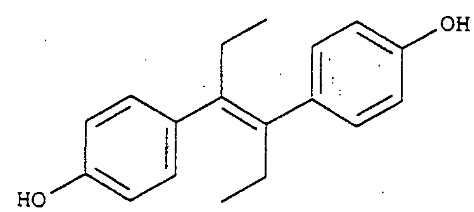

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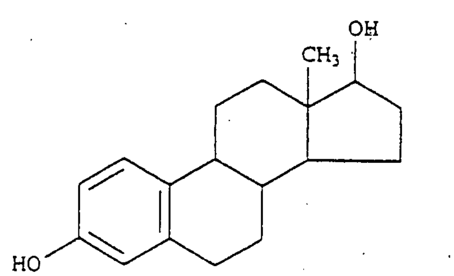

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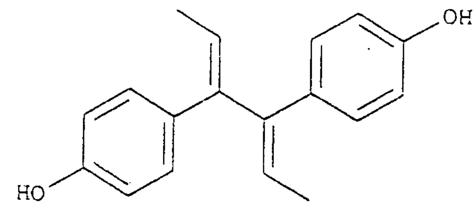
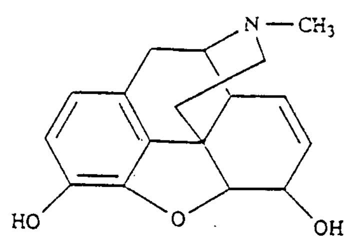


(74)

6 FRAGMENTS OF THE LEAD MOLECULE

Design of fragments of a lead molecule is based on the premise that lead molecules, especially polycyclic natural products, may be more structurally complex than is necessary for optimal pharmacologic effect. Buried within the structure of such a lead compound is a pharmacophoric moiety that, if it can be clearly defined, may be "dissected out" to result in a biologically active, simpler molecule that may itself be used as a lead in further analog design. A bond disconnection strategy may be employed, in which bonds in the chemical structure are broken or removed to destroy one or more of the rings. The result may be a valuable drug that is more accessible (through chemical synthesis) than the original lead molecule. A disadvantage to this strategy of drug design is that greater flexibility may be introduced into a rigid molecule, and the conformational integrity of the pharmacophore that may have existed in the original lead molecule is compromised or lost, sometimes at the expense of activity/potency. There may be a similar destruction of chiral centers, which may be undesirable.

Morphine (75) can be cited as a lead molecule to illustrate fragment analog design.



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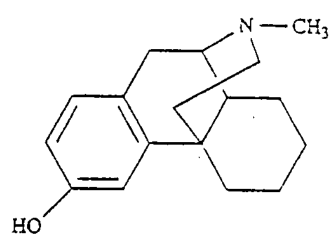

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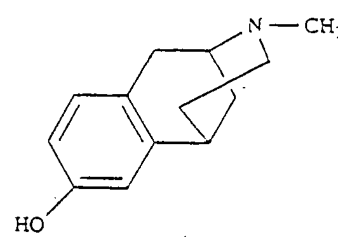

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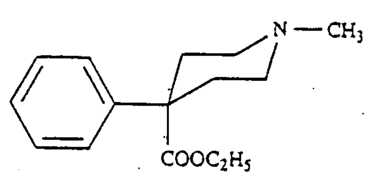

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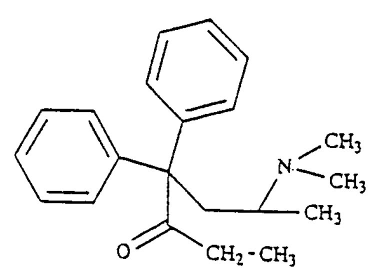
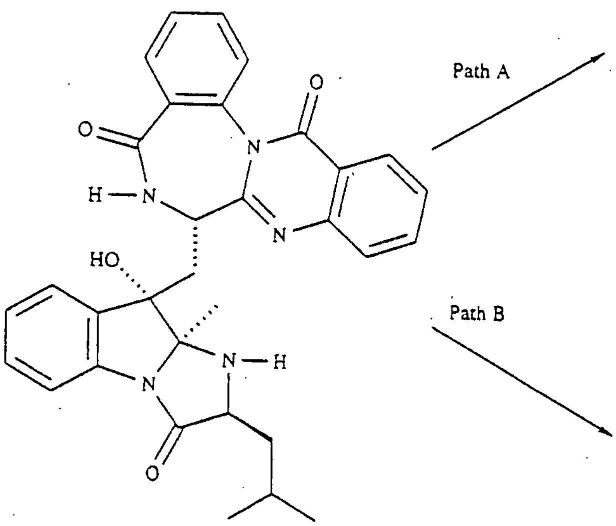


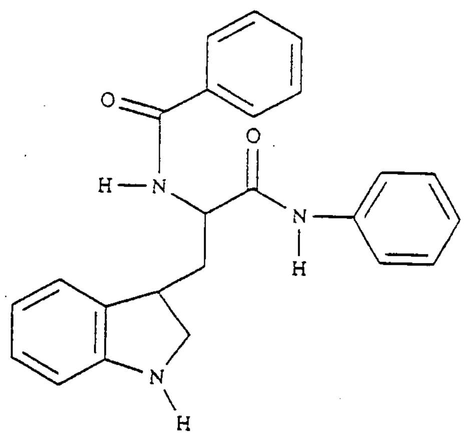
(79)

The analgesic pharmacophore of morphine has been defined (37) as the basic nitrogen, an aromatic ring (the "A" ring) three carbon atoms removed from the nitrogen, and a quaternary carbon adjacent to the aromatic ring, which provides a region of molecular bulk (37). A bond disconnection strategy involved disruption of the hydrofuran ring to give rise to morphinan ring derivatives, e.g., levorphanol (**76**), whose pharmacological effects closely parallel those of morphine (38). Further simplification of the morphine ring system led to benzomorphan derivatives, typified by metazocine (77) in which morphine like narcotic analgesic activity is retained. Finally, 4-phenylpiperidine derivatives typified by meperidine (**78**) and the noncyclic system methadone (**79**) present the putative analgesic pharmacophore with a seemingly minimal number of extraneous atoms. These simple compounds retain narcotic analgesic activity. It must be noted, however, that the discovery of analgesic activity in 4-phenylpiperidine derivatives was not a result of a systematic structure-activity study of the morphine molecule, but was serendipitous (39).

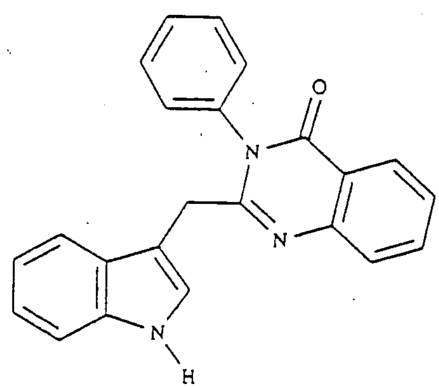
Asperlicin (**80**), a potent cholecystokinin-A antagonist, was subjected to two different bond disconnection strategies, as indicated (40).



(80)



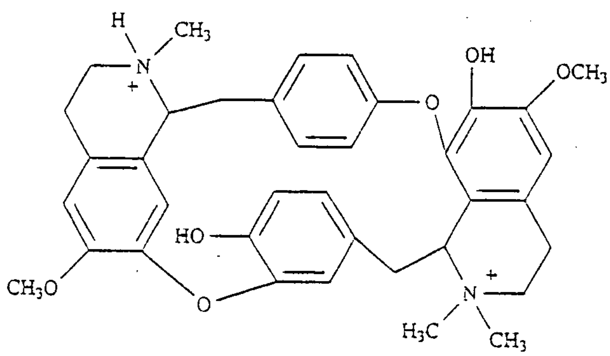
(81)



(82)

Path A leads to tryptophan derivatives (81), some of which are potent cholecystokinin antagonists (41). Some quinazolinone derivatives (82) of disconnection pathway B showed extremely high potency and excellent selectivity as cholecystokinin-B receptor subtype ligands (24). A combination of X-ray crystallography and computer-based molecular modeling was utilized in the decision making process in the bond disconnection (24) and in the design of specific target molecules.

The myoneural blocking pharmacophore in *d*-tubocurarine (**83**) includes the two cationic heads (a quaternary ammonium group and a protonated tertiary amine); the cationic heads are separated by ten atoms (nine carbons and one oxygen).



(83)

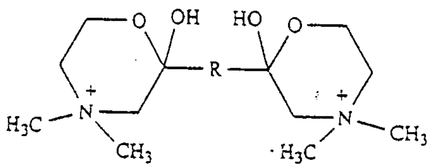
$$(CH_3)_3\overset{+}{N}-(CH_2)_{10}-\overset{+}{N}(CH_3)_3$$

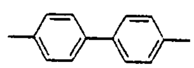
(84)

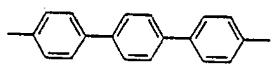
Based on these parameters, a simple molecule, (decamethonium) (**84**), in which two trimethylammonium heads are separated by 10 methylene groups to approximate the internitrogen distance in *d*-tubocurarine, was designed independently by two groups of investigators (42, 43). This synthetic fragment/analog of *d*-tubocurarine exhibits a high degree of potency and activity in production of flaccid paralysis of skeletal muscles, superficially like that of the lead compound. However, *d*-tubocurarine's myoneural blockade is of the nondepolarizing type whereas decamethonium produces a depolarizing type of skeletal muscle blockade. This fundamental difference in mechanism of action is due in part to the flexibility of the decamethonium molecule compared with *d*-tubocurarine. The difference in mechanism of action of the two myoneural blocking agents results in a considerable difference in the spectrum and severity of side effects and in the technique of employment in clinical practice. In all types of analog design, changes in chemical structure may result in changes in mechanism of action, even though the chemical nature of the pharmacophoric group may not be altered.

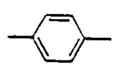
7 VARIATION IN INTERATOMIC DISTANCES

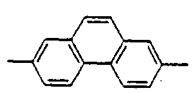
Alteration of distances between portions of the pharmacophore of a molecule (or even between other portions) may produce profound qualitative and/or quantitative changes in pharmacological actions. In a series of congeners of hemicholinium (**85**), the central biphenyl portion of the molecule was changed to terphenyl (**86**) and to *p*-phenylene (**87**). Both changes resulted in profound loss of myoneural blocking activity (44). This result was ascribed to alteration of the interquaternary nitrogen distance of 14.4 Å in hemicholinium (**85**) (which was assumed to be the optimum for myoneural blockade) to 18.4 Å in the terphenyl analog and to 10.2 Å in the *p*-phenylene analog. The central biphenyl "spacer" in hemicholinium (**85**) was changed to a 2,7-disubstituted phenanthrene (**88**), *trans,trans*-4,4-bicyclohexyl (**89**), and 2,2′-dimethylbiphenyl (**90**). In all three of these systems the 14.4-Å interquaternary distance in hemicholinium (**85**) was maintained; all of these congeners were quali-

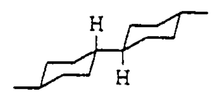


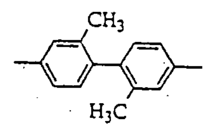
(85) R = 

(86) R = 

(87) R = 

(88) R = 

(89) R = 

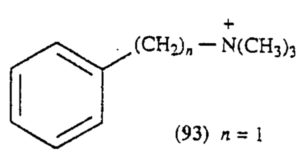
(90) R = 

(91) R = $-(CH_2)_6-$

(92) R = $-(CH_2)_7-$

tatively and quantitatively similar to hemicholinium in inhibition of neuromuscular transmission. Conformational analysis of the polyalkylene congeners (**91** and **92**) demonstrated that when the flexible polyalkylene chain is maximally extended and in a staggered conformation, the interquaternary distance in the hexamethylene congener (**91**) is approximately 14 Å, and in the heptamethylene congener (**92**) it is approximately 15 Å. Both compounds exhibited hemicholinium-like inhibition of neuromuscular transmission, although they were less potent than hemicholinium (45). This diminution of potency might be ascribed to the compromising of another structural parameter in the hemicholinium molecule: the rigidity of the central biphenyl spacer unit that maintains the internitrogen distance.

In a series of phenylalkylenetrimethylammonium derivatives (**93**)–(**95**), nicotinic agonism is maximal when $n = 3$ [compound (**95**)].



(**93**) $n = 1$

(**94**) $n = 2$

(**95**) $n = 3$

It was concluded (46) that a moiety (benzene ring) with high electron density three or four single bond lengths (approx. 6 Å) from the cationic center is a requirement for nicotinic agonism in the series (46).

In α,ω-bis-trimethylammonium polymethylene compounds (**96–99**), maximal activity for blockade of autonomic ganglia resides in those derivatives where $n = 5$ or 6 (**96** and **97**) (47, 48)

$$(CH_3)_3\overset{+}{N}-(CH_2)_n-\overset{+}{N}(CH_3)_3$$

(**96**) $n = 5$ (**98**) $n = 16$

(**97**) $n = 6$ (**99**) $n = 18$

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Ganglionic effects drop drastically when $n = 4$ or 7. These observations have been rationalized on the basis of attainment of optimal interquaternary distance in the penta- and hexamethylene congeners for optimal interaction with ganglionic receptor subsites. Remarkably, as the number of methylene groups in compound (**96**) is further greatly expanded, a high level of ganglionic blocking potency returns. The hexadecyl and octadecyl congeners (**98**) and (**99**) are approximately four times as potent at autonomic ganglia as the penta- and hexamethylene compounds. As was mentioned previously, polymethylene bis-quaternary systems, in which the cationic heads are separated by 10 methylene groups, have potent effects at myoneural junctions and little action at autonomic ganglia. Thus extension of a *bis*-quaternary polyalkylene molecule from 5 or 6 methylenes to 10 produces a pharmacological change from ganglionic blockade to myoneural blockade, and further extension to 16 or 18 methylenes results in loss of myoneural effects and a return of ganglionic blocking action.

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